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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,046	01/17/2006	Kristen E. Belmonte	PU60398	3933
23347	7590	03/12/2008	EXAMINER	
GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY, MAI B475 FIVE MOORE DR., PO BOX 13398 RESEARCH TRIANGLE PARK, NC 27709-3398			RAHMANI, NILOOFAR	
			ART UNIT	PAPER NUMBER
			1625	
			NOTIFICATION DATE	DELIVERY MODE
			03/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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LAURA.M.MCCULLEN@GSK.COM

Office Action Summary	Application No. 10/565,046	Applicant(s) BELMONTE ET AL.	
	Examiner NILOOFAR RAHMANI	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>01/17/2006, 05/22/2007, 01/23/2008</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-13 are pending.

2. ***Priority***

This application is filed on 01/17/2006, which is a 371 of PCT/US04/22947, filed on 07/16/2004, which claims benefit of 60/487,981, filed on 07/17/2003.

3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification lacks enablement for a compound of Formula (I). There is no working example in the instant specification for the compounds of formula (I). Therefore, the specification lacks enablement for the compounds of Formula (I).

4. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compound to alter the gene expression and therefore to treat any and all known or unknown diseases. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In *re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims.
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to method of inhibiting the binding of acetylcholine to its receptors in a mammal or a method of treating a muscarinic acetylcholine receptor mediated disease using the compound of formula (I).

The state of the prior art: "Repeated antigen exposure induced airway inflammation, IgE/IgG1 responses, epithelial changes, collagen deposition in the lungs, subepithelial fibrosis associated with increases in the amount of transforming growth factor (TGF)- β 1 in BAL fluid (BALF), and bronchial hyperresponsiveness to acetylcholine. The number of eosinophils in BALF was significantly correlated with TGF- β 1 production in BALF and the amount of hydroxyproline. Furthermore, significant correlations were found between these fibrogenic parameters and the bronchial responsiveness. Prolonged antigen exposure can induce airway remodeling associated with BHR in sensitized mice, which included collagen deposition beneath the basement membrane and goblet cell hyperplasia/hypertrophy." (Tanaka et al., *Inflammation Research*, Vol. 50, 2001, pages 616-624).

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970)

indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating a pharmacological condition in a subject.

Amount of guidance/working examples: Applicant provides no guidance for using a compound of Formula (I) could treat any and all known or unknown diseases. Nor does applicant identify what diseases are treatable by therapeutically effective amount of a compound of Formula (I).

The breadth of the claims: The breadth of claims is drawn to method of inhibiting the binding of acetylcholine to its receptors in a mammal or a method of treating a muscarinic acetylcholine receptor mediated disease using the compound of formula (I).

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for treating diseases associated with effective amount of a compound of Formula (I) is efficacious, one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity

by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claims 5-13, for inhibiting the binding of acetylcholine to its receptors in a mammal or a method of treating a muscarinic acetylcholine receptor mediated disease using the compound of formula (I) is efficacious, have been enabled by the instant specification.

5. *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

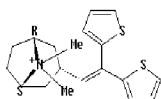
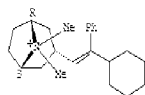
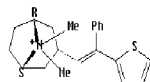
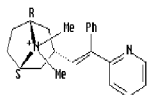
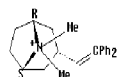
Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Zirkle et al., Journal of Medicinal & Pharmaceutical Chemistry, 1962, Vol. 5, pages 341-56. Zirkle et al. disclosed the instant claimed compounds

RN 102924-25-4

CN 8-Azoniabicyclo[3.2.1]octane, 3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-,

Art Unit: 1625

bromide,

• Br⁻**RN** 106801-38-1**CN** 3a-(b-Cyclohexylstyryl)-8-methyltropanium bromide• Br⁻**RN** 107422-05-9**CN** 8-Azoniabicyclo[3.2.1]octane, 8,8-dimethyl-3-[2-phenyl-2-(2-thienyl)ethenyl]-, bromide,• Br⁻**RN** 107894-96-2**CN** 8-Azoniabicyclo[3.2.1]octane, 8,8-dimethyl-3-[2-phenyl-2-(2-pyridinyl)ethenyl]-, bromide,• Br⁻**RN** 108042-35-9**CN** 8-Azoniabicyclo[3.2.1]octane, 3-(2,2-diphenylethenyl)-8,8-dimethyl-, bromide,• Br⁻

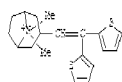
Therefore, the instant claim is anticipated by Zirkle et al.

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6. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Zirkle et al., US 2800482. Zirkle et al. disclosed the instant claimed compounds

RN 110377-10-1

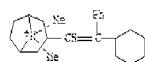
CN 3-(2,2-Di-2-thienylvinyl)-8-methyltropanium bromide



• Br⁻

RN 119040-93-6

CN 3-(b-Cyclohexylstyryl)-8-methyltropanium bromide



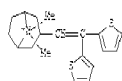
• Br⁻

Therefore, the instant claim is anticipated by Zirkle et al.

7. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Zirkle et al., US 2800478. Zirkle et al. disclosed the instant claimed compounds

RN 110377-10-1

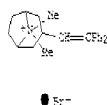
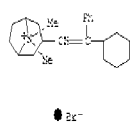
CN 3-(2,2-Di-2-thienylvinyl)-8-methyltropanium bromide



• Br⁻

RN 118801-08-4

Art Unit: 1625

CN 3-(2,2-Diphenylvinyl)-8-methyltropanium bromide**RN** 119040-93-6**CN** 3-(b-Cyclohexylstyryl)-8-methyltropanium bromide**RN** 124138-73-4**CN** 3-(2,2-Diphenylvinyl)-8-methyltropanium p-toluenesulfonate (6Cl)

. Therefore,

the instant claim is anticipated by Zirkle et al.

8. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

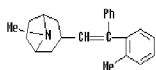
Claims 1-4 are rejected under 103(a) as being unpatentable over Yu et al., Yaoxue Xuebao (1983), 18(10), 766-74.

Determination of the scope and content of the prior art (MPEP §2141.01)

Yu et al. disclosed analogous compound,

RN 88543-21-9

CN 8-Azabicyclo[3.2.1]octane, 8-methyl-3-[2-(2-methylphenyl)-2-phenylethenyl]-



Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and the prior art compound is that the instant compound is the salt of the prior art compound.

Finding of prima facie obviousness-rational and motivation (MPEP §2142.2143)

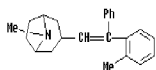
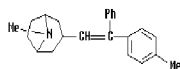
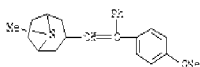
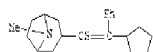
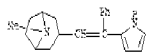
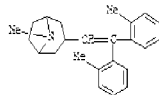
All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

9. Claims 1-4 are rejected under 103(a) as being unpatentable over Ran et al., Yaoxue Xuebao (1984), 19(5), 361-6.

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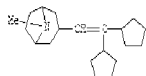
Determination of the scope and content of the prior art (MPEP §2141.01)

Ran et al. disclosed analogous compound,

RN 88543-21-9**CN** 8-Azabicyclo[3.2.1]octane, 8-methyl-3-[2-(2-methylphenyl)-2-phenylethenyl]-**RN** 98042-92-3**CN** 8-Azabicyclo[3.2.1]octane, 8-methyl-3-[2-(4-methylphenyl)-2-phenylethenyl]-**RN** 98042-93-4**CN** 8-Azabicyclo[3.2.1]octane, 3-[2-(4-methoxyphenyl)-2-phenylethenyl]-8-methyl-**RN** 98042-94-5**CN** 8-Azabicyclo[3.2.1]octane, 3-(2-cyclopentyl-2-phenylethenyl)-8-methyl-**RN** 98042-95-6**CN** 8-Azabicyclo[3.2.1]octane, 8-methyl-3-[2-phenyl-2-(1H-pyrrol-2-yl)ethenyl]-**RN** 98042-96-7**CN** 8-Azabicyclo[3.2.1]octane, 3-[2,2-bis(2-methylphenyl)ethenyl]-8-methyl-**RN** 98042-97-8

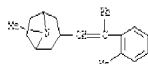
Art Unit: 1625

CN 8-Azabicyclo[3.2.1]octane, 3-(2,2-dicyclopentylethenyl)-8-methyl-, hydrochloride



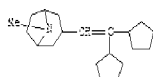
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CN 8-Azabicyclo[3.2.1]octane, 8-methyl-3-[2-(2-methylphenyl)-2-phenylethenyl]-



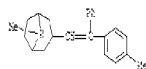
RN 98043-09-5

CN 8-Azabicyclo[3.2.1]octane, 3-(2,2-dicyclopentylethenyl)-8-methyl-



RN 98988-11-5

CN 8-Azabicyclo[3.2.1]octane, 8-methyl-3-[2-(4-methylphenyl)-2-phenylethenyl]-



Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and the prior art compound is that the instant compound is the salt of the prior art compound.

Finding of prima facie obviousness-rational and motivation (MPEP §2142.2143)

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

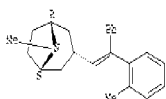
10. Claims 1-4 are rejected under 103(a) as being unpatentable over Zhang et al., Yaoxue Xuebao (1985), 20(10), 752-8.

Determination of the scope and content of the prior art (MPEP §2141.01)

Zhang et al. disclosed analogous compound,

RN 100345-20-8

CN 8-Azabicyclo[3.2.1]octane, 8-methyl-3-[2-(2-methylphenyl)-2-phenylethenyl]-



Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and the prior art compound is that the instant compound is the salt of the prior art compound.

Finding of prima facie obviousness-rational and motivation (MPEP §2142.2143)

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

11. Claims 1-4 are rejected under 103(a) as being unpatentable over Wu et al., Zhongguo Yaowu Huaxue Zazhi (1993), 3(1), 23-6.

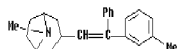
Determination of the scope and content of the prior art (MPEP §2141.01)

Wu et al. disclosed analogous compound,

RN 153307-16-5

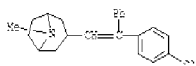
Art Unit: 1625

CN 8-Azabicyclo[3.2.1]octane, 8-methyl-3-[2-(3-methylphenyl)-2-phenylethenyl]-



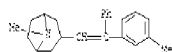
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CN 8-Azabicyclo[3.2.1]octane, 3-[2-(4-chlorophenyl)-2-phenylethenyl]-8-methyl-



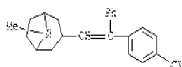
RN 153307-19-8

CN 8-Azabicyclo[3.2.1]octane, 8-methyl-3-[2-(3-methylphenyl)-2-phenylethenyl]-



RN 153307-20-1

CN 8-Azabicyclo[3.2.1]octane, 3-[2-(4-chlorophenyl)-2-phenylethenyl]-8-methyl-



Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and the prior art compound is that the instant compound is the salt of the prior art compound.

Finding of prima facie obviousness-rational and motivation (MPEP §2142.2143)

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

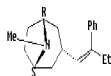
12. Claims 1-4 are rejected under 103(a) as being unpatentable over Zirkle et al., Journal of Medicinal & Pharmaceutical Chemistry, (1962), 5, 341-56.

Determination of the scope and content of the prior art (MPEP §2141.01)

Zirkle et al. disclosed analogous compound,

RN 99673-47-9

CN Tropane, 3a-(b-ethylstyryl)-, hydrochloride



Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and the prior art compound is that the instant compound is the salt of the prior art compound.

Finding of prima facie obviousness-rational and motivation (MPEP §2142.2143)

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on 571-272-0867. The

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fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI

D.MARGARET SEAMAN

02/12/2008

PRIMARY EXAMINER

GROUP 1625

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625